Dear Madam,

As an introduction, and before answering your questions point by point, let me give you a summary of the context in which your article will appear in the journal Science.

The arrival of the Covid 19 epidemic in Europe:

Scientists who did not follow the official narrative of panic and impossibility were harassed. This was, incidentally, the subject of a 3-page article in Nature (Appendix 1 and 1b) on Scientifics under attacks, which showed the different types of attacks that these scientists may have suffered, including death threats, attempts to discredit the science of those who did not agree with governments, with sometimes surprising aggressiveness.

As far as we are concerned, the day after I said that Chloroquine was an option, to which I will return, I began to receive, in the middle of the night, death threats. The person who made them has been identified: Professor RAFFI, who had considerable conflicts of interest, having received 600,000 euros in the last few years, as could be identified on Euro for Docs. He was also convicted by the Criminal Court of Nantes, which is the city where he lives.

Then, another individual belonging to the health corps filed a complaint with the Public Prosecutor of Marseille for the use of chloroquine. This case was closed by the Prosecutor without further action (Appendix 2). Then I was attacked by the Council of the Order of Physicians. The conclusion of the Council of the Order, in December 2021, was that I had committed no fault in prescribing hydroxychloroquine for patients with Covid 19, since this fell within the freedom of doctors to prescribe according to their knowledge.

Subsequently, I was the victim of a small conspiracy to make it appear that we were carrying out an illegal trial of treatment for tuberculosis, which justified an investigation carried out for 8 months by 9 people from 3 national inspectorates, which showed that there had never been an abnormal trial on tuberculosis, and which, all in all, identified 3 possible violations after we submitted 75,000 documents on all trials:

1. One in a trial on the evaluation of *Tropheryma whipplei* in diarrhoea. There were 34 informed consents missing out of nearly 4000 (less than 1%), out of a study that had been carried out several years earlier.
2. The second considered a difference in interpretation in a study done among medical students, who came to ask for advice on the risks of infection in tropical travel, and carried out self-sampling of anuses and vaginas, before and after the trip, to detect multi-resistant

bacteria. It should be noted that the detection of multi-resistant bacteria is part of good medical practice, that self-sampling of the anus is not invasive, but that there had been ambiguity about the meaning of vaginal self-sampling.

3. The 3rd study, which seemed to be problematic, was the use of urinalysis, collected for other tests, to be evaluated by new techniques.

These 3 cases are under investigation, but I am hopeful that these 3 issues will be closed.

It should be noted that no complaint has ever been filed against IHU members for the treatments, that no deaths have been deplored by the hydroxychloroquine treatment [1] and that no real fraud has been detected among the 800 signals that have been sent by PubPeer. Most of the signals concern an interpretation of the regulations, which is not French law, and Mrs Bik's interpretations of similarity in the case of gels which a more in-depth analysis showed that they were different. In all these elements, it would be interesting to know what is the motive that would lead the most cited researchers in the world to make forgeries on gels that do not change the meaning of the message. Essentially, our work has been to make the discovery (more than 1000 bacteria in the last 10 years) the description of a whole group of new viruses, the giant viruses, the culture of bacteria hitherto considered unculturable, such as *Rickettsia felis* and *Tropheryma whipplei.*

All of this data has been combined with tens of thousands of genetic sequences that are currently on GenBank and available, and of course, this is impossible to invent. In practice, the essentials we do cannot give rise to fraud under any circumstances because all our documents are available to everyone. We are, I believe, the only ones who have made 100% of our data available for the treatment of COVID with hydroxychloroquine. The bacteria we have described are deposited in bacteria banks that are available and can be used by all researchers around the world. It is quite astonishing to see the multiplication of hundreds of criticisms that are then analysed as fraud, on analyses of the regulations that do not make sense concerning human waste, as is explained in the annex on elements recently confirmed by our Minister of Health.

It should be noted that, at that time, PubPeer was already talking about 600 ethical misconducts and that none of them was retained. In practice, there is a bunch of stalkers, which is now perfectly analyzed. I am attaching the articles in French (Appendix 3 and 4), which you will easily translate with Google, concerning the composition of this cyber harassers. The implementation of a plan to disgrace me scientifically, which you can see is partially working since you are writing to me, is partly directed by Elisabeth BIK, whose letter (Appendix 5) she sent to most of the scientific publishers and against whom I have filed a complaint, as well as the other harassers. The investigation of his case is ongoing

in France, like that of PubPeer. Some of these authors have published, as you have noted, an article for which we have obtained an "Expression of concern", and which I hope will be retracted shortly.

Currently, we are officially continuing with investigations that are underway, Mrs. Elisabeth Bik, PubPeer, Lonnie Besançon who are part of this bunch of harassers. So I suggest you be careful given the fact that this investigation is ongoing and I'm not worried about the outcome, given the fact that the defamation is obvious.

As for hydroxychloroquine, it's a drug that I've been using for 30 years. In 100% of medical books, you will find the use of hydroxychloroquine in the treatment of Q fever and Whipple's disease, which are treatments that I developed, at the dosage that I used in Covid without ever having had any therapeutic problems including cardiac clinical adverse event [1,2] . I have treated several thousand people and carried out several thousand hydroxychloroquine assays in my own laboratory, so I know the kinetics perfectly. For the past ten years, hydroxychloroquine has been recognized as a potential antiviral, because its major mechanism of activity, the alkalinization of lysosomes, is a non-specific activity that is exerted on bacteria (Coxiella, Tropheryma Whipplei) as well as on parasites (malaria) or viruses. The evaluation of hydroxychloroquine had already been carried in vitro out on SARS 1, and Anthony Fauci, at the time, considered hydroxychloroquine to be the treatment for SARS, until the epidemic died spontaneously. At the beginning of the SARS-CoV-2 outbreak, the Chinese quickly published that the virus was susceptible to hydroxychloroquine and remdesivir. In view of the fact that remdesivir is known to cause kidney failure, as demonstrated during its use in the treatment of Ebola disease, in which treatment had to be discontinued due to its inefficacy and dangerousness, the treatment that remained usable was hydroxychloroquine.

As soon as we had our first strain isolated in Marseille, Professor LA SCOLA tested hydroxychloroquine and azithromycin, which is an antibiotic that has quite frequent activity on RNA viruses [3]. We were able to find that with a concentration of 0.3 µ /ml, hydroxychloroquine inhibited the multiplication of the virus. The average concentration obtained, with the dosage we use to treat Q fever and Whipple's disease, is 600 mg/day ie 1µg/ml (which is the same dosage that is used by millions of people for the treatment of lupus and rheumatoid arthritis). The safety of hydroxychloroquine, at these doses, has long been known, and one publication reported the absence of heart problems in nearly one million people taking hydroxychloroquine regularly, for several months or years, at these doses with rheumatic pathology in Lancet Respiratory diseases [4]. Thus, the safety of hydroxychloroquine, at these doses, is perfectly known. It’s in vitro efficacy on viruses has been confirmed by at least a dozen publications. On the contrary, a whimsical publication was published in the Lancet [5], reporting 10% mortality. This post is a fake pure and simple and the article was immediately retracted. The data

doesn't exist and can't exist. There were more cases in this study than there had been in the whole of Australia, compared to what was reported in the paper. Another paper by the same authors in the New England of Medicine reported the ethnicities of French patients. However, this is forbidden by law in France. You can't report the ethnicity of patients. It is also interesting that this, which is a notorious forgery, which influenced the decision of our Minister of Health and the WHO, has not been the subject of a judicial investigation, to my knowledge. And you are interested in us who treated the patients, rather than in these people who did not see the patient and who made publications that are fakes, which we do not know whether or not they were financed by the pharmaceutical industry.

Furthermore, Mrs BIK claims in her letter, and you imply, that we have neo-colonialist attitudes towards the countries of the South, particularly the African countries. In reality, the Foundation was essentially built to ensure and to assist in the training of students from the South in master's and thesis, in total, more than 200 students at the IHU, coming from the South (Middle East, Africa, Arabia, Vietnam), by sponsoring them. This work has always been done in agreement with the local teams and the samples have been evaluated by students who came to do their thesis. In a number of cases, these theses were carried out under joint supervision an according the Nagoya rules when implemented in the country. The only country for which we did not have an ethics committee was Niger, which has been in an unstable political situation for an extremely long time, and in which an ethics committee was only created in 2016. However, the student from Niger, who brought and started her work, had been sent to us by the Dean of the Faculty of Science, and in her thesis jury was the Medical Director of her hospital and the Rector of her University, who has since become Minister of Higher Education. My relations with Senegal are long and have been very constructive, since I co-directed, with a Senegalese investigator, a research unit in Senegal, and the interest of the work we have carried out in terms of prevention and therapeutics has led the President of Senegal to give me the greatest decoration in Senegal: The Lion of Senegal, by making me a Commander in 2022. These accusations of exploitation and neo-colonialism are totally erroneous and testify to the complete lack of knowledge of the subject by Mrs. BIK, who conveys them.

Concerning ethical problems, I attach an analysis made by the lawyer present in the IHU, who is Associate Professor of Health Law, on the evolution of bioethics laws in France (Appendix 6). In all the countries that adopted Roman law and then Napoleon law, waste, including these issued from humans is considered as an object, and is not part of medical research. This is the case with feces, urine, and sputum. This is part of the Napoleonic Code and was recalled in 1976 in French law. We had the opportunity, in 2023, to have the question officially put to the Minister of Health. His legal services replied that human waste was a thing, not part of medical research. Thus, work on

anonymized human waste is not, in the eyes of French law, part of medical research, which explains the discrepancy between PubPeer claims and the results of the very long investigation of which we were the victims in 2022. Most of the things we've been criticized for in PubPeer are not within the scope of the law. Regarding the use of stool to search for bacteria, we asked two ethics committees: one local and the other national (CNRS). Both told us that this was not biomedical research, since we were looking for bacteria (which are not humans) in waste, and that as long as the origin of the waste was anonymized, it did not represent medical research. This led us, since the publishers requested it, to repeat the validation number by a local ethical committee each time as the worked is strictly the same. It should be noted that ethics committees have no legal existence in France, where everything is managed by the so-called Jardé law. Anything outside the scope of the Jardé law, and that is not in the field of research, does not fall under the purview of an ethics committee. Regarding the use of waste, leftovers from samples taken for other reasons (diarrhea, blood tests for antibodies), French law does not provide for informed consent, but the patient can report an objection on a register that is made available to him in the hospital, and he benefits from systematic information on this possibility.

But the non-objection regarding healthy donors, which has been used for feces, comes from the remains of harvests, resulting from donations to perform fecal transplants. We were the first in France to do fecal transplants officially, and in accordance with the law. Fecal graft remnants from the samples, from healthy subjects who had undergone a battery of tests to avoid grafting with pathogens, could be used to perform microbial cultures.

You can see that neither you, nor the people at PubPeer, nor Mrs. Bik are able to assess what is in the law and what is not in the law because you do not know the French law. We give you the precise context of the French law, which in addition, the laws of bioethics have not stopped changing over time. So, there are things that we are accused of that are simply within the framework of French law. This explains why, once again, despite the 800 reports from PubPeer, and after 8 months of investigations and 75,000 documents analyzed, the mission sent by the Ministry (to prove that we were doing an illegal trial on tuberculosis!) found only the 3 elements that I shared with you, which are rather laughable because asking to have kept 4000 informed consents on paper for a study that was 12 years old [6] and to have lost 0.3% of them borders on the ridiculous and shows the degree of malevolence to which we have been subjected.

In the same vein, it should be noted that after we had sent the ASM the evidence that the images that had been presented in an article were not a manipulation, the person in charge of ethics asked us to send him the original of a 20-year-old western blot. This again shows that the ethics people in

these journals have a scientific knowledge that is extremely rudimentary. Westen Blots that are kept as they are for 20 years must probably be exceptional.

Regarding our activities in scientific journals, I do not think that you are lucid about the scientific level of the people who participated in the IHU. So, in 2021, 9 people were part of Clarivate's Highly Cited, including myself in two fields. As a result of the harassment of which we were the victim, Clarivate, the following year, withdrew the names of 8 of the 9 people. And this year, 3 new ones, bringing the number of Highly Cited over 3 years to 12, were added, two of which were later removed by the protest of the harassing bunch. This reflects the importance of the scientific production, and the number of citations from the University Hospital Institute. As such, I have long been the most cited infectious disease microbiologist in Europe and, relatively recently, the most cited in the world, ahead of Martin Blaser and Nicholas J White. My H factor on Google, which is easily verifiable is at 210. Most of the older journals were run by academics, and the editors were usually famous researchers. As such, as I am the researcher who has published the most in the journals of the American Society of Infectious Diseases, the one who had published the most in the journals of the infectious disease society of America, of the American Society of Microbiology (including the Journal of Clinical Microbiology), the one who has published the most in the Lancet Infectious Diseases, in the European Journal of Clinical Microbiology and Infectious Diseases, as one of the most published in Emerging Infectious Diseases, and one of the most published in Nature Microbiology Reviews, have been invited to serve on the boards of many, many journals. The fact that you are part of a journal does not in any way prevent you from sending publications that you do not edit yourself, but that are managed by other publishers. The journal of which I was editor-in-chief, Clinical Microbiology and Infection, for several years, received from me only two original articles that were edited by co-editors unrelated to me. The other articles that I published in this journal, while I was editor-in-chief, were editorials, as it is natural for the editor to write them, and this was validated by the head of the Society. It should be noted that, for one of the most prestigious journals in the world, the PNAS, the academics themselves submit a certain number of publications that they want to see published in the PNAS, without this appearing particularly dangerous. On the other hand, I think that there is a drift with the multiplication of the number of journals which tends towards having administrative staff as EIC, who have no skills, neither in science nor in law, which leads to a mediocrization of the quality of published science, and a concentration on problems that are more administrative than scientific. No fraud has ever been detected in the 3500 publications I have made. Mrs. BIK, who thinks she is an expert in gel analysis, uses rudimentary tools. I had the opportunity to respond on PubPeer to his accusations. A study is in the process of being published, carried out by experts in image analysis, which shows that it confuses resemblance and similarity out of malice.

Finally, the comments on the management of the IHU are defamatory and I suggest you beware of them. I have already had the opportunity to have defamatory remarks about me in the journal Sciences, which led, on the one hand, to a letter of correction, and on the other hand, I attacked the author who had written it and we had an amicable settlement agreement with compensation.

The IHU, contrary to what you say, is the place where absenteeism and transfer requests are the lowest of the 2 establishments to which the IHU belongs. The IHU, in fact, is only a foundation intended to finance research and students. All but 10 of the IHU's employees are hospital or university employees and they have unions and can easily be transferred from one department to another. In fact, the rate of transfer or sick leave of these staff is the lowest of the 2 establishments to which they are attached. These elements were also notified during the inspection visit. The rate of absenteeism is a third lower than that of the hospital staff of the CHU to which we are attached, as well as the university staff, all these data are quantified, verifiable and not based on gossip and slander.

Finally, as far as the countries we work with are concerned, the implementation of a new microbiota analysis technique, culturomics, has made it possible to isolate nearly 1000 new species of microbes. Many bacteria have been named after the country of origin of the sample, or the country of the investigator or even the name of a foreign researcher who discovered one of these microorganisms.

In reality, all the data you collect has a single source. The fact that we have proposed an early treatment in Covid, which has given results that have been confirmed in other studies (in Italy, Belgium) and of which you can see the summary on the only exhaustive site of report on early Covid 19 therapeutics, on earlyc19.com, our last study on the 30,000 cases [1], that we treated ourselves, who are not fictitious patients but patients registered in the University Hospital of Marseille, who received a treatment whose data were validated by the central pharmacy of the hospitals of Marseille, in whom we measured what the mortality was, thanks to data independent of the national collection of mortality of people in France, which was able to show that the mortality of hospitalized patients, oxygen-dependent in the Infectious Diseases and Microbiology Unit of the University Hospital of Marseille, located in the IHU building, was 7%, i.e. the lowest in the world currently published, for those who were treated with hydroxychloroquine without any patient’s complaints [1]. Hydroxychloroquine is one of the drugs that every doctor can prescribe if he considers it to be the best treatment at the time, he examines the patient. This data was confirmed in 2023 by the Director-General of Health, Professor Salomon, now at the WHO, who confirmed that we had every right to treat patients with hydroxychloroquine, if we thought it was the most appropriate treatment.

Pr D Raoult

Point by point response to questions.

Dear Prof. Raoult,

I'm a journalist at the American magazine *Science*. We will soon be publishing a story that details critiques of, and investigations into, research carried out by you and other researchers at the IHU Marseille.

I would very much like to include your perspective in this story. Do you have any response to the following questions ?

1. Your research has been at the centre of a growing controversy over the past four years. It has been reported that the Marseille prosecutor is investigating claims of criminal violations at the IHU. Have you heard from the prosecutor? Do you have any comment on this investigation?

   See general comments and context in the introduction.

2. Critics have raised a range of concerns about research and publication practices at the IHU, including that IHU researchers frequently publish in journals where they also serve as editors. Many researchers say this is an editorial conflict of interest. What is your response to this?

   See general comments and context in the introduction.

3. Researchers have also raised concerns about ethical approval in IHU research. In August 2023, a group of researchers published a paper in which they show that 248 IHU studies—investigating different questions in different populations—used the same ethical approval number (09-022). Why did these studies all use the same approval code? Do you agree that this is a breach of research ethics?

   The paper by Frank and collaborator published by Springer Nature reports that more than a hundred papers used the same IRB number. This is perfectly true but they confuse the IRB which in France (the authors are French) is an authority called CPP and which validates a priori prospective studies called bioethical research corresponding to research on man framed by the bioethics law and the local ethical committees which are advisory committees that give an ethical opinion and in particular

on the qualification of the study between study under the bioethics law or study not covered by bioethics law. These local ethics committees are not mandatory in France (see above) made up of experts (dean of the faculty, specialist in medical ethics, lawyer or legal advisor, etc.). The "IRB" number reported in this article is a local ethics committee opinion number that dates back to 2009 and which gives a favorable opinion for the diversified analysis of bacteria in human feces collected either in the context of care or in the context of waste because, as indicated in the opinion, there is no specific sampling for research. Once again, it is therefore not surprising for world experts in stool culturomics that several articles refer to a single analysis of this type. A reply concerning the substance of this article has also been submitted to the publisher of the newspaper by a regulatory and "fair play" channel, that of the letter of reply to the editor.

On the form of this article, **we have requested the retraction of this article to Springer Nature** on two grounds; 1- major conflict of interest not allowing the authors a clear and independent analysis of the facts and 2- that the results are unreliable in relation to a superficial analysis biased by conflicts of interest. We cannot go into further detail as an investigation by Springer Nature's ethics team is underway for conflicts of interest and breach of the research integrity code. However, we inform you that after analyzing the content of the Franck et Al study, we plan to initiate legal proceedings against the authors for slander and lying.

This article is directly related to the cyber harassment we have been victims of since 2020. We are not the only ones, the cyber harassment of scientists, during this health crisis, has become the preferred means of expression of activist groups, claiming to be the guarantors of scientific integrity, grouped under various associations such as Citizen4Science or the FaKe Med collective, in which we find individuals, most of whom are people in need of academic recognition (unfinished science thesis or people who have not been able to pursue research), and who find in this activity of denunciation, the opportunity to take their title test. Others, including some colleagues, have major conflicts of interest. For example, Mr Mé H, who is one of the colleagues who filed a complaint against us to the college of physicians (complaint without follow-up) received 165,900 euros from Pfizer between 2020 and 2022 to finance an internet blog on which he spends his time denigrating us. There is a reason here to influence his discourse and his objectivity on the efficacy of hydroxychloroquine! Apart from the conflicts of interest of some, scientific integrity, of which they claim to be the guarantors, has not always been their practice. Some of them are being prosecuted for having taken blood samples without consent from demonstrators, (**Alexander Samuel**, co-author of the Frank.al article), others have scientific articles in which we can doubt compliance with the regulations, and which have been pinpointed by Pubpeer without providing an answer to the clarifications asked to

them, such as **G Barriere** and **V Saada** . They are also co-authors of this article. One can therefore have a big doubt about the scientific integrity of these activist and cyber-harassing groups, at the center of which Mrs. BIK, an emblematic figure of scientific integrity herself, is not above suspicion. (appendix 7 and 8). Here are some examples of activist activity of Mr Franck Fabrice claiming that he is proud to be a stalker with is a real breach into research integrity code as stipulated in the The European Code of Conduct for Research Integrity REVISED EDITION 2023 (appendix 9 10 and 11)

A complaint was filed in 2021 with the public prosecutor of Marseille, France, on behalf of several complainants, targeting several criminal offenses. A preliminary investigation (still ongoing, according to our information) has been opened. The lawyers in charge of this case are Brice GRAZZINI and Ludovic HERINGUEZ

In addition, several of the authors of the Franck et Al study (Alexander SAMUEL and **Lonni BESANCON**, who have constantly multiplied the accusations of scientific fraud and breaches of ethics against Professors Raoult and Chabriere, in particular, are on trial with Professors Raoult and Chabriere, in the context of various parallel criminal cases currently being dealt with by the courts, and potentially likely to have direct and indirect links with the facts mentioned in the complaint of April 28, 2021.

4. These researchers say that many of these studies were conducted in African countries, and that there are no details or limited details on whether local ethical bodies had given ethical approval. The journal *Scientific Reports* also retracted two IHU papers last year, citing a lack of evidence of ethical oversight in Niger and Senegal. Was there approval from local ethical bodies for these studies? If so, why was there no evidence of it?

This accusation shows once again the degree of ignorance of these activists regarding the French legislation and that of the countries with which we work. This reinforces the fact that this article has only one purpose: pure malice.

Research ethics regulations have not evolved at the same speed in different countries. In particular, those who were at war or had other priorities did not develop ethical rules until very recently. The particular case of Niger (see above) deserves to be clarified, on the one hand because it is representative of the situation in other developing countries and, on the other hand, because at the time of writing, two publications on the analysis of the microbiota of severely malnourished children had been withdrawn by the publisher.

Indeed, in Niger, a 2013 decree of the Ministry of Education requires prior administrative authorization for research. Article 11 stipulates that for specific subjects: " *It is understood that the establishment of the administrative authorization for research is strictly subject to the opinion of the ethics committee set up for this purpose.*" But Niger's National Committee for Health Research Ethics was only created in 2016 (decree 2016-644/PRN/MSP), and the stool samples sent to the IHU-MI for analysis by Dr. Souleymane Brah, a doctor at the Niamey hospital, were taken in 2014, when the Nigerien CNERS did not yet exist. Prior to the creation of CNERS, there was a National Consultative Ethics Committee (CCNE) but, as indicated in the National Strategic Plan for Health Research published by the Nigerien Ministry of Health in 2013, the legal framework governing its operation was very weak and its funding non-existent. In the absence of a functioning ethics committee and legislation specifically governing the ethics of human health research, it was not possible in 2014 for Nigerien doctors collaborating with the IHU-MI to have a written document from an official ethics committee.

On the other hand, the authors claim that Prof. Adehossi, director general of the Niamey hospital where the samples were taken and a member of the Faculty of Life Sciences, certified that the study complied with Nigerien laws and the Declaration of Helsinki.

The situation in Senegal is somewhat different, with ethical legislation in place since 2001. Our collaborator in Senegal was the on the board of the first IRB in 2001 and since then all the research that we have done in Senegal have a favorable approval of an IRB.

It is therefore necessary to consider the specific context of certain developing countries before suspecting ethical fraud. The information is accessible to all, including in this article entitled: "National Ethical Guide in Sub-Saharan Africa on the Collection and Use of Human Biological Specimens: A Systematic Review" published in 2016 [7] . Tables 2 and 3 indicate whether countries have ethical legislation in place and, if so, whether it includes specific clauses for the reuse or transfer of biological materials. **These tables confirm that at the time the study on child malnutrition was carried out, Niger did not have any legislation, regulations or instructions concerning the ethics of human health research. It is regrettable that the authors did not delve into the subject in depth before submitting their paper, thus risking retractions on the basis of incomplete or erroneous information.**

5. Many of the studies that use repeated ethical approval codes involved vulnerable populations, including homeless people, refugees, and students. Critics call the use of these participants without proper ethical approval “outrageous". Do you agree that this is a breach of ethics? Do you feel that the IHU has a duty of care for these vulnerable populations?

The homeless are a population that suffers and dies, especially from infectious and parasitic diseases. We have an agreement with two homeless shelters and took care of the fantastic epidemic of lice observed in these people that was concomitant with an outbreak of *Bartonella quintana* infection that we had discovered in patients who had been hospitalized for endocarditis. In fact, 5 to 10% of homeless people had chronic *Bartonella quintana* bacteremia, which naturally develops into fatal endocarditis. So, in agreement with the national authorities that had made studies on fragile populations legal, we set up work to firstly detect tuberculosis and treat it in hospital, and secondly, detect chronic *Bartonella quintana* infections when patients presented to the hospital emergency room. This is called medicine. It should be noted that after a few years, we managed to eradicate the *Bartonella quintana* epidemic [6]. We are extremely proud to have cared for the homeless. You should know that the essential work for years of infectious disease specialists has been to treat the poorest and most disadvantaged populations, combined with the treatment of patients from tropical areas. What these people, who are particularly evil, are reproaching us for is that we are doing the heart of the job for which most of us have been appointed Professor of Infectious and Tropical Diseases.

Studies in fragile populations were excluded until the 80’s under French law. Since then, these populations have been considered a population in which research is possible and legal. All of our studies in homeless populations have received appropriate advice from a CPP (IRB) because in fact they were most of them studies approved and funded by the French government (PHRC). Of course, we have a duty of care for these populations, and this is the essential reason why studies should be carried out to provide them with better care and better living conditions. We studied diseases transmitted by lice in this population and eradicated lice and associated diseases in this population.

Again, these are malicious accusations from this small group of stalkers. They are only a handful of malicious people but very active on the networks. Moreover, the scientific journals are beginning to react because it does not fool anyone. They pride themselves on forcing scientific journals to retract articles, accusing them of doing their job poorly and of letting articles with ethical problems or duplicate images slip through. They used Pubpeer to perpetrate their abominable slander that is finally making them famous.

6. Early on in the pandemic, before the IHU had conducted any studies with HCQ, you released videos claiming that the pandemic would quickly be over because Covid could be treated with HCQ or chloroquine phosphate. What made you so confident?

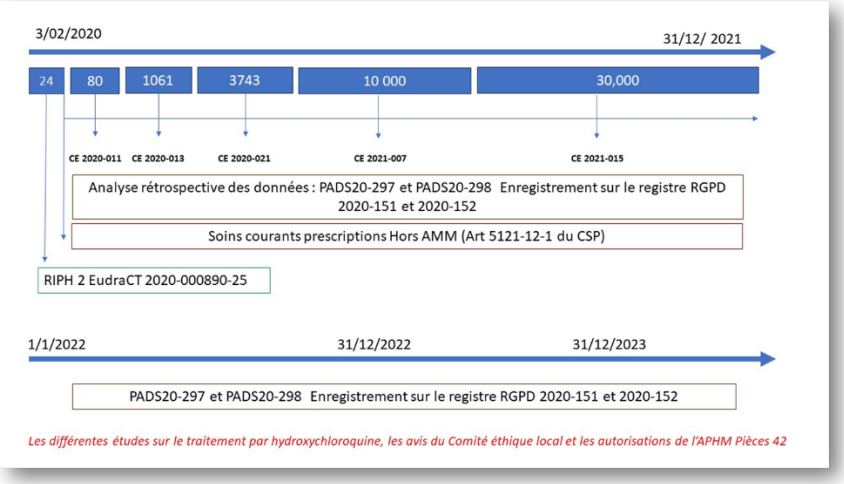
   See general comments and context in the introduction.

7. Your March 2020 paper in *International Journal of Microbial Agents* stated that patients were followed for fourteen days. The paper was submitted for publication on 16 March, meaning that data collection must have begun on 2 March. However, ethical approval was granted by a CPP and the ANSM on 5 and 6 March. Did you begin data collection before ethical approval was granted?

   As I understand you do not read the paper and only repeat was "researchers" said in the media. This answer is very simple. In the protocol as stated in the text of the paper we planned to test the patient at D14. But due to the surprising results we did an intermediated analysis at day 6 that we published. The complete data analysis with the D14 PCR are published in clinicaltrails.org. Since this time, we confirmed on a larger sample of test that the effect of HCQ is optimal at day 5-7. In conclusion patients were included after the CPP advice on March 5, 2020. The complete data are available in European Clinical trials register.

8. Your April 2020 paper in *Travel Medicine and Infectious Disease* described treating 80 hospitalized COVID-19 patients with hydroxychloroquine. You and your co-authors described this research as retrospective, but other researchers have said that giving a patient a drug to test its effectiveness makes it a clinical trial. How do you respond to that ?

   In reality, as indicated below, we have only carried out one prospective study under the bioethics law with all the necessary regulations (RIPH2, EudraCT 2020-000890-25).



We refused for simple ethical reasons; "No patient should be treated by drawing lots between a placebo and a non-toxic molecule that you have elements in the scientific literature to say could be effective" to continue studies on the drug and we have considered as of April 2, 2020 that we will treat patients "off label". However, giving an "off-label" treatment does not prevent a retrospective evaluation of the quality of care and the efficacy of the drug. In French regulations, this is called a retrospective observational study on medical data and does not fall under the law of bioethics.

It is important to understand what the French law on bioethics is before criticizing colleagues.

What is the Jardé Law? This is the law that governs Research Involving the Human Person (RIPH), formerly known as bioethics law. In its article R1121-1 of the Public Health Code amended by Decree No. 2017-884 of 9 May 2017 in force at the time of the facts, it defines what is RIPH and what is not RIPH and is therefore not subject to the law.

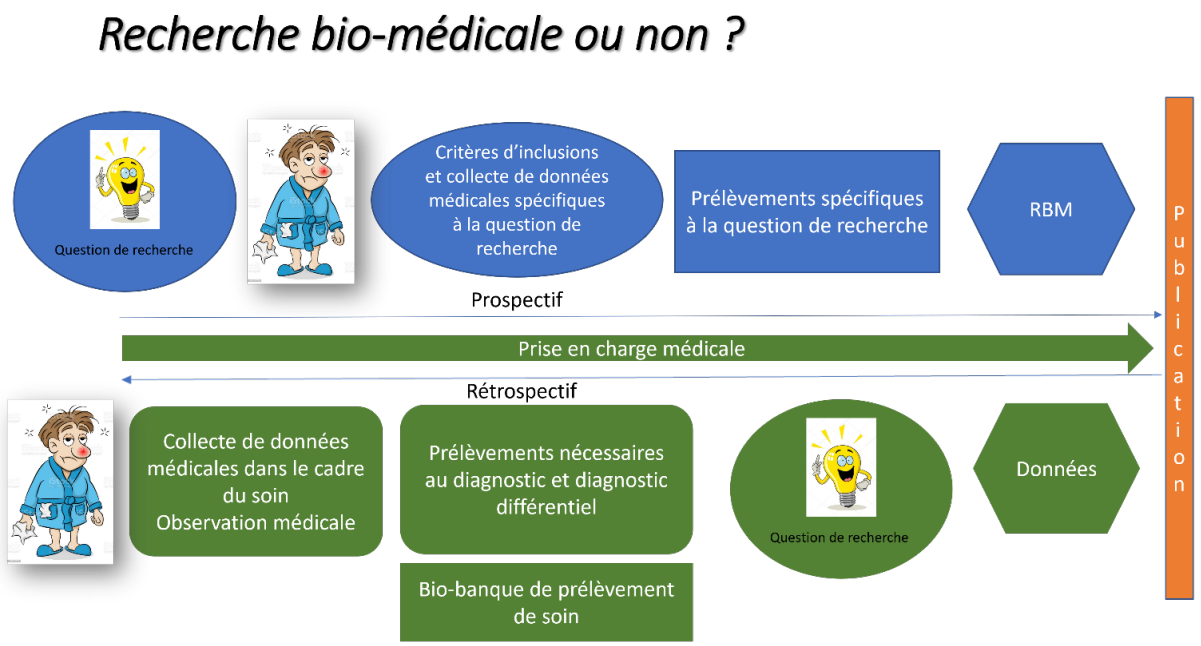
Paragraph 3 states:

"3° Research involving the human person ***within the meaning of this*** *Title shall not include research having a public interest purpose of research, study or evaluation in the field of health* ***conducted exclusively on the basis of the exploitation of the processing of personal data*** *referred to in I of Article 54 of Law No. 78-17 of 6 January 1978, as amended, relating to data processing, files and freedoms and which fall within the competence of the expert committee for research, studies and evaluations provided for in paragraph 2 of II of the same article."*

The diagram below, which is a slide used as a learning support for our students, summarizes the situation.

CASE N°1 blue path-The research question can only be answered by the implementation of a specific treatment, sampling or care and a patient is sought to experiment with this specific treatment, diagnosis or care. Inclusion criteria are necessary to select the right patient for the experiment and therefore not all patients will participate in the research, but only those who will be selected. We are therefore in a prospective framework for which the patient will serve as a "guinea pig" to answer a research question and the acts are performed for the same purpose. This is biomedical research subject to the law (Jardé in this case) whose qualification RIPH 3, RIPH2 and RIPH1 is related to the level of risk for the patient.

CASE N°2 green path- The patient enters a care process and the collection of medical information and data is necessary for his care, it is a matter of medical observation and is recorded in a care database or medical information system currently available in all hospitals. The samples taken from this patient are necessary for his management for its diagnosis, differential diagnosis, possible drug interactions and biological monitoring of its treatment and the evolution of its disease. In addition, the bottom of the tube taken as part of the treatment is bio-banked to correct any errors. The research question arises after the treatment, and to be solved it will use the data collected in the databases. This is a retrospective observational study using not the patient but only the patient's data collected during care. This is not a biomedical study and is not subject to the law. The use of this data requires compliance with its processing and declaring this compliance to the GDPR Data Protection Regulation register.



9. Your October 2023 paper in *New Microbes and New Infections* describes treating COVID-19 patients with hydroxychloroquine until December 2021, even though the temporary licence for hydroxychloroquine as a COVID-19 treatment was withdrawn in May 2020. A group of academics called this an "illegal clinical trial", saying that this shows that the IHU continued to prescribe the drug to large numbers of patients for more than 18 months after the license was withdrawn, without approval from a CPP and the ANSM. What is your response to this?

Once again, they speak without knowing. They mix it all up. The CPP has nothing to do with off-label prescribing, which is governed by the Public Health Code and the Code of Ethics. You will see that all this is a machination set up by some who have a lot of conflict of interest and who have above all an interest in saying that hydroxychloroquine could have saved thousands or even hundreds of thousands of lives. We hope that this story will be brought to the conclusion in international courts and that journalists will finally open their eyes.

Chloroquine and hydroxychloroquine have never had a "license", i.e. a marketing authorization for COVID. Its use was temporarily authorized by decree (this means that it could be prescribed under the responsibility of the state), but like "off-label" drugs in the USA, it is possible to use "off-label" drugs under certain conditions and under the responsibility of the prescribing doctor (Article L. 5121-8 of the Public Health Code and Art 8 of the Code of Ethics). This is the case for 80% of hospital pediatric medicines and for more than 40% of prescriptions in general in France. This is a needs as this is the only way to propose a treatment to a patient when none proven efficient exist.

Here are the evolutions of the decrees authorizing the prescription of hydroxychloroquine under the responsibility of the state.

Decree 2020-314 of March 25, 2020 in its "*Art. 12-2. – By way of derogation from Article L. 5121-8 of the Public Health Code, hydroxychloroquine and the lopinavir/ritonavir combination may be prescribed, dispensed and administered under the responsibility of a doctor to patients suffering from covid-19, in the health establishments that take care of them...* »

was followed by the

Decree 2020-337 of 26 March 2020 where it was added *"These prescriptions are made, after a collegial decision, in compliance with the recommendations of the High Council of Public Health and, <u>in particular</u>, the indication for patients with oxygen-requiring pneumonia or organ failure*."

was followed by the

Decree 2020-548 of May 11, 2020 which in its *"Art. 19. – By way of derogation from Article L. 5121-8 of the Public Health Code, hydroxychloroquine and the lopinavir/ritonavir combination may be prescribed, dispensed and administered under the responsibility of a doctor to patients suffering from covid-19, in the health establishments that care for them, as well as, for the continuation of their treatment if their condition allows it and with the authorization of the initial prescriber, at home. These prescriptions are made, after a collegial decision, in compliance with the recommendations of the High Council of Public Health and, in particular, the indication for patients suffering from oxygen-requiring pneumonia or organ failure.* »

and finally, the

Decree 2020-630 of 26 May 2020 which restores the prescription of chloroquine as it was originally.
Art. 6-2. – The proprietary medicinal product PLAQUENIL ©, in compliance with the indications of its marketing authorization, and hydroxychloroquine-based preparations may only be dispensed by dispensing pharmacies in the context of an initial prescription issued exclusively by specialists in rheumatology, internal medicine, dermatology, nephrology, neurology or pediatrics or in the context of a renewal of a prescription issued by any doctor ".

This does not mean that the "off label" prescription as authorized by Article L. 5121-8 of the Public Health Code and Article 8 of the Code of Ethics is not possible. In July 2020, the Council of the Order of Pharmacists made a clarification on this subject, confirming what we said above.

In fact, prescribing hydroxychloroquine as an off-label treatment was perfectly legal in France, as these different elements have shown, and the current government has tried to pass a law to make the prescription of off-label drugs against government instructions as a crime punishable by prison and fines. This law has just been rejected by the House of Representatives after having been rejected by the Senate and advised against by the Council of State. This latest rejection dates from February 13, 2023 and shows that if the current government wanted to promote such a law , the prescription of hydroxychloroquine was in no way illegal.

10. The American Society for Microbiology retracted six of your papers in January, citing a lack of CPP approval and saying that the research was a breach of the Declaration of Helsinki as well as French law. Do you have any comment on this? Do you agree that these studies lacked proper ethical approval?

An independent expertise has been requested by our university. Only one expert wished to carry out this expertise. The CPP opinions had not been forwarded by our university to the expert. We responded point by point to the expert's comments so that our university could forward the response to the ASM. This response was never sent to the DSO. They retracted the articles simply on the basis of the expertise without contradictory report, which is illegal in France.

11. Nearly 50 further studies have been flagged by PLoS with expressions of concern because of ethical problems, and Elsevier has announced that it is investigating ethical concerns in IHU papers. Do you have any comment on this?

One of these retracted paper for example was dealing with lice collected onto homeless people and we were accusing not to ask homeless if they agree to collected lice on their clothes because lice live

in clothes. This paper at the submission period asks this question we answer that lice do not belong to any body and that they were not part of the human body, and that regulation does not mention the needs for that. Their ethic team said that this was ok and they publish the paper. And now because they have been questioned by the team of activist, they questioned again this paper and even with answering the question pose an expression of concern. This is just ridiculous.

12. A 2022 ANSM report describes a "disaster of regulatory obligations" at the IHU, such as missing ethical approval, a lack of understanding of ethical regulations, and missing consent forms. You released a statement at the time stating that the IHU had reached a different conclusion to the ANSM – do you have anything further to add to that?

    See general comments and context in the introduction.

13. The French government's auditing bodies released a report in 2022 highlighting these same issues. They conclude that you tightly held the reins of power in the IHU and that staff were under immense pressure to prescribe HCQ even after authorization had been rescinded. They also interviewed several staff members who talk about "often brutal, sometimes humiliating management." Do you have any response to the findings of this report?

    See below.

14. Many academics who have raised these issues have accused you, your colleagues, and your supporters of harassment and bullying. What is your response to this?

    In France, in hospitals, it is not the doctors who rate or promote the staff entrusted to them. For the promotion of doctors, this is done at the national level by the CNU, independently of the medical hospital managers. For non-medical staff, it is the administration that organizes this outside the decision of the medical managers. Thus, concerning the appointment of hospital practitioners and research professors, this is done by elected commissions (the Dean's Council or the Hospital Council) for which the candidates present themselves. Of course, the opinion of the head of department is sought, but it is not a decision-making decision. In practice, the pressure exerted by heads of department on staff who do not report to you, neither for their career progression nor for their appointment, is extremely weak. Considering the fact that some colleagues may have complained, this cannot be surprising in a research and care centre with more than 800 people. Following a protest of this type, a list was put to the vote, including those who agreed with the organization and those who did not. Those who agreed with the organization garnered 97% of the vote. One must be

wary of anecdotal backbiting reports that do not reflect practical, everyday reality. Moreover, recently two investigations were carried out on this subject, one by a law firm specializing in harassment requested for the Director of the Hospital, the conclusion was that no harassment nor bulling was identifiable at this stage. In addition, in January 2024, a survey conducted in different university hospital sites was conducted in the IHU on well-being at work and the team's conclusion was that this was the site in which the return in the perception of well-being at work was the most important.

We hope that these comments will be useful to you in preparing a more relevant, objective, fair, unbiased, contradictory article that allows Science journal readers to form their own opinion based on the facts and not on the words repeated inexhaustibly by the press and the media.

Thank you for entrusting us with this answer.

Prof Didier Raoult

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